Case Reports

Cushing's Syndrome in a Patient With Suppressible Hypercortisolism and an Empty Sella

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THE INCIDENTAL FINDING of an empty sella turcica is common even in asymptomatic patients.[1] To date, there have been only three reports of patients with hypercortisolism, elevated plasma adrenocorticotropic hormone (ACTH) level, Cushing's disease and an empty sella.[2-4] In two of these patients,[2,3] a small pituitary adenoma was found at operation in an otherwise empty sella. The third patient[4] did not have a pituitary surgical procedure. In this report, the patient presented with cushingoid features, and partial pituitary hypofunction, an empty sella and an inappropriately elevated plasma ACTH level with partially suppressible hypercortisolism were recorded. Surgical exploration of the pituitary fossa, however, failed to show a discrete adenoma. A small posterior rim of intrasellar tissue was found that contained nests of abnormal basophils. No ectopic source for ACTH could be identified. A pituitary surgical procedure was not successful in controlling the patient's disease but she did respond to a combination of aminoglutethimide and cyproheptadine hydrochloride.

Report of a Case

The patient, a 60-year-old obese Korean woman, had hypertension dating to 1976, treated with salt restriction, thiazides and β-blockers. In 1981 she gained 11 kg (25 lb) in weight in a year, and an increasingly round and pigmented facies developed. The patient first presented to the University Hospital (Seattle) in February 1982 because of increasing shortness of breath and abdominal and back pain. She had mild facial hirsutism, acne, central adiposity, a small buffalo hump and hyperpigmentation over the dorsum of her hands and fingers. Despite blood pressures of 140 to 180/100 to 120 mm of mercury, her fundi were normal and an electrocardiogram did not show evidence of left ventricular hypertrophy or strain. The patient's blood pressure was difficult to control on increasing doses of diuretic, β-blocker and, eventually, minoxidil.

An overnight suppression test with 2 mg of dexamethasone resulted in an 8 AM serum cortisol level of 9μg per dl (normal less than 5). A plasma ACTH level was 80 pg per ml (normal less than 80) and 24-hour urinary 17-hydroxycorticosteroid excretion was 41 mg (normal 2.5 to 10). While she was taking dexamethasone (0.5 mg four times a day for two days) her 8 AM serum cortisol level fell from 43 μg per dl to 27 μg per dl and her 24-hour urinary 17-hydroxycorticosteroid excretion was 32 mg. High-dose dexamethasone (2.0 mg four times a day for two days) resulted in a further decrease of her urinary 17-hydroxycorticosteroid excretion to 26 mg per 24 hours. Visual fields were normal. Tomograms showed the sella turcica to be normal in size and shape, but the bones were demineralized. Computed tomography (CT) of the head (Figure 1) showed low density in the sella turcica with the exception of a posterior rim of soft tissue. Metrizamide enhancement (Figure 2) showed an empty sella with a small mass at the base of the sella.* Computed tomography of the abdomen showed both adrenal glands enlarged but otherwise there were no abnormalities. Spine films showed generalized mineral loss with compression fractures of T-11 and L-1. Chest x-ray films showed an elevated right hemidiaphragm and no mass lesions and suggested the presence of generous amounts of fat in the mediastinum.

Additional endocrine testing yielded the following values: plasma luteinizing hormone, 6 mIU per ml (premenopausal 4 to 30) despite her postmenopausal state; plasma follicle-stimulating hormone, 4 mIU per ml; serum estradiol, 29 pg per ml. A serum prolactin level (30 ng per ml) was slightly raised (normal 0 to 25). Tests of thyroid function showed no abnormalities: thyroxine, 5.1μg per dl (normal 4.1 to 11.3); triiodothyronine resin uptake, 46% (normal 33 to 45); thyroid-stimulating hormone, 1.9 μIU per ml (normal 0 to 6.5). Urinary excretion of 5-hydroxyindoleacetic acid was 6.3 mg per 24 hours (normal less than 10.0).

Because the patient appeared to have pituitary-dependent Cushing's syndrome and review of the literature suggested that even in the case of an empty sella, adenomas could usually be found in such patients, in June 1982, she underwent a transsphenoidal exploration of the pituitary fossa. A small amount of abnormal-appearing fluid was aspirated from the fossa. Multiple biopsy specimens were obtained from a small rim of fibrous-appearing tissue at the base of the sella. The

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*Douglas Stewart, MD, Department of Cardiology, was involved in various aspects of the workup and management of this patient, and computed tomography and reconstructions were provided by Nicole Bolander, MD, Department of Radiology.

ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone
CT = computed tomography

sella was otherwise empty of tissue.* Histologic examination showed a large amount of fibrous tissue and nests of abnormal basophilic cells interspersed with occasional nests of normal-appearing acidophilic cells. The basophilic cells had large amounts of granulated cytoplasm and frequent central vacuolization with displacement and deformation of the nucleus (Crooke's changes). She remained persistently cushingoid and hypertensive and easy bruisability developed as well as generalized muscle weakness of a proximal distribution. Several new vertebral compression fractures developed at T-12 and L-2 through L-5. Follow-up serum cortisol and ACTH levels were 31 μg per dl (4 PM) and 71 pg per ml, respectively, in July 1982. Bilateral adrenalectomy was considered as a treatment option at this point but because of the patient's obesity and poorly controlled hypertension, the procedure was deferred. Unfortunately, a breast abscess developed that did not respond to local incision, drainage and antibiotics, requiring debridement under general anesthesia. Postoperatively she had high-output cardiac failure and hypoventilation. It was elected to institute treatment of her Cushing's disease (see Figure 3) with aminoglutethimide, cyproheptadine and pituitary irradiation with the hope of decreasing the morbidity associated with her cushingoid state and facilitating her postoperative recovery. Her serum cortisol level fell from 68 μg per dl to 29.5 μg per dl but the patient died in September 1982, several days after an unexplained respiratory arrest. A postmortem examination was not done.

Discussion

Of patients presenting with pituitary hyperfunction and an empty sella, most have coexisting prolactinomas or growth hormone-secreting tumors.[5-10] A most unusual syndrome of elevated plasma ACTH level in the presence of an empty sella, normal cortisol dynamics and no cushingoid features has been reported in two patients.[11,12] In one of these two cases, gel filtration chromatography showed nearly all of the immunoreactive ACTH to be a large-molecular-weight form, which the authors speculated to be of reduced biologic activity. Another unusual case of an elevated, non-suppressible plasma ACTH level and an empty sella has been reported in a patient with Addison's disease who remained hyperpigmented despite adequate glucocorticoid replacement.[13] To date, there have been only three cases reported of patients with hypercortisolism, elevated plasma ACTH level, Cushing's disease and an empty sella.[2-4] In two of these patients, a small pituitary adenoma was identified at operation in an otherwise empty sella, while in the third pituitary sella exploration was not done.

The present case is notable in several respects. On the one hand, this is one of only four reported cases of Cushing's disease and an empty sella. In contrast to the previous reports in which pituitary surgical pro-

*The surgical procedure was carried out by William Kelly, MD, Department of Neurosurgery, and the histologic studies were done by Cheng Mei Shaw, MD, Department of Pathology.

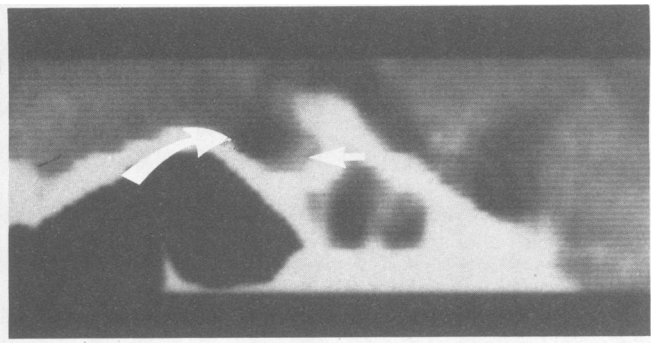

Figure 1.—Computed tomography of the head with contrast (diatrizoate meglumine) enhancement. Shown is a lateral computer reconstruction of the sellar area. The **curved arrow** points to the hypodense empty sella containing a small posterior rim of tissue (**straight arrow**).

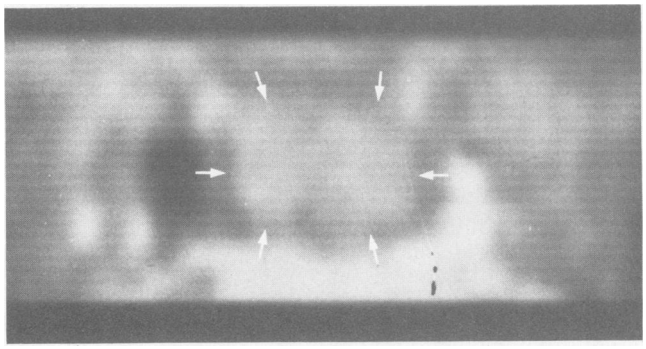

Figure 2—Computed tomography of the head with intrathecal administration of metrizamide. Shown is a coronal computer reconstruction of the sellar area. Metrizamide (hyperdense area outlined by **arrows**) completely fills the sella, confirming the presence of an empty sella. The hypodense area to the left is a pneumatized sphenoid sinus.

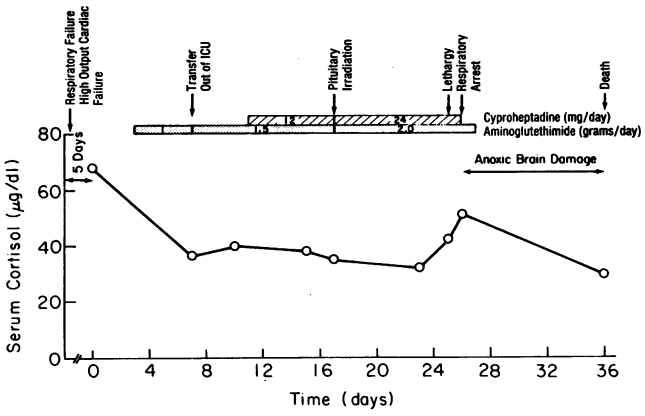

Figure 3.—A summary of the biochemical response to treatment as assessed by serum cortisol levels in the patient during her final hospital stay. Major clinical developments and therapeutic interventions are indicated. ICU = intensive care unit.

cedure was done, however, the small amount of pituitary tissue in the otherwise empty sella had basophilic hyperplasia and no adenoma. In addition, partial pituitary hypofunction is suggested by plasma gonadotropin levels that were inappropriately low for her postmenopausal state. Thyroid function was normal. Several management issues arose during the course of this patient's illness that deserve comment. Selective venous catheterization would have been helpful in establishing the pituitary as the source of inappropriate ACTH production. In a case of pituitary-dependent Cushing's and an empty sella, it is probably still warranted to surgically explore the pituitary fossa for a possible adenoma. Bilateral adrenalectomy remains, however, a reasonable treatment alternative.

The question of whether this patient had Cushing's disease or Cushing's syndrome on another basis cannot ultimately be settled without a postmortem examination. The weight of the evidence suggests a pituitary basis. The factors supporting a primary pituitary aberration are the inappropriate rise in the ACTH level (though still within the normal range) in the presence of extreme hypercortisolism and its partial suppressibility. Other possible causes for Cushing's syndrome appear to be reasonably excluded. Documentation by CT scan of enlargement of both adrenal glands rules out a unilateral adrenocortical adenoma as the source of this patient's hypercortisolism. An ectopic source for ACTH is also unlikely for several reasons. The patient's long clinical course (six years), negative findings on a chest x-ray film, normal 24-hour urinary excretion of 5-hydroxyindoleacetic acid and partially suppressible hypercortisolism are inconsistent with an ectopic source for ACTH. Furthermore, the ACTH level in this paraneoplastic syndrome tends to be much higher than occurred in this patient. The failure of high-dose dexamethasone to suppress urinary 17-hydroxycorticosteroid excretion by at least 50% may argue against pituitary-dependent Cushing's disease, but 15% to 30% of these patients fail to suppress to this degree.[14]

This case also has potentially interesting implications concerning the natural history of Cushing's disease. If this patient's primary defect was at the level of the hypothalamus resulting in inappropriate stimulation of the pituitary, this would have caused development of a pituitary adenoma, ACTH hypersecretion and cushingoid features. Infarction of the adenoma may have then occurred, resulting in an empty sella. Of other possible causes of an empty sella, a developmentally incomplete sellar diaphragm cannot be completely excluded, whereas involution of a previously hypertrophied and overstimulated pituitary due to end-organ failure appears highly unlikely.

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Homonymous Hemianopia Due to Cerebral Air Embolism From Central Venous Catheters

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PERCUTANEOUS PLACEMENT of a central venous catheter has become a routine bedside procedure. Immediate mechanical complications include direct trauma to nerves, arteries and pleura and embolization of air or catheter fragments. Delayed complications are primarily infectious and thrombotic in nature.[1,2] The following reports of cases illustrate an unusual complication of central venous catheters—homonymous hemianopia due to cerebral air embolism—and highlight the need to implement precautions to prevent this complication.

Reports of Cases

CASE 1. The patient, a 60-year-old man, was admitted for control of malignant hypertension and unstable angina. Evaluation showed diffuse arteriosclerosis, which included carotid and renal artery disease as well as 70% occlusion of his left anterior descending and right coronary arteries. The patient underwent right carotid endarterectomy in April 1981 and coronary-artery-bypass graft operation three weeks later. Both procedures were uneventful. Five days after the cardiac operation the patient was transferred to the ward with a left subclavian venous catheter in place.

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